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## The association between albuminuria and long-term renal risk

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## CHAPTER 2

# Drug-induced reduction in albuminuria is associated with subsequent renoprotection: A meta-analysis

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## Abstract

### Introduction:

Albuminuria has been proposed as a surrogate end point in randomized clinical trials of renal disease progression. Most evidence comes from observational analyses showing that treatment-induced short-term changes in albuminuria correlate with risk change for end-stage renal disease (ESRD). However, such studies are prone to selection bias and residual confounding. To minimize this bias, we performed a meta-analysis of clinical trials to correlate the placebo-corrected drug effect on albuminuria and ESRD to more reliably delineate the association between changes in albuminuria and ESRD.

### Methods:

MEDLINE and EMBASE were searched without language restriction for clinical trials reported between 1950 and April 2014. Included trials had a mean follow-up of at least 1000 patient years, reported ESRD outcomes, and measured albuminuria at baseline and during follow-up. Meta-regression was performed to assess the association between drug effects on albuminuria and ESRD.

### Results:

Twenty-one clinical trials involving 78,342 patients and 4183, ESRD events were included. Median time to first albuminuria measurement was 6 months. Fourteen trials tested the effect of renin-angiotensin-aldosterone-system inhibitors (RAASi) and 7 trials tested other interventions. We observed variability across trials in the treatment effect on albuminuria (range -1.3% to -32.1%) and ESRD (range -55% to +35 risk change). Meta-regression analyses revealed that the placebo-adjusted treatment effect on albuminuria significantly correlated with the treatment effects on ESRD: for each 30% reduction in albuminuria, the risk of ESRD decreased by 23.7% (95%CI 11.4 to 34.2;  $P=0.001$ ). The association was consistent regardless of drug class ( $P=0.73$ ) or other patient or trial characteristics.

### Conclusion:

These findings suggest albuminuria may be a valid substitute for ESRD in many circumstances, even taking into account possible other drug-specific effects that may alter renal outcomes.

## Introduction

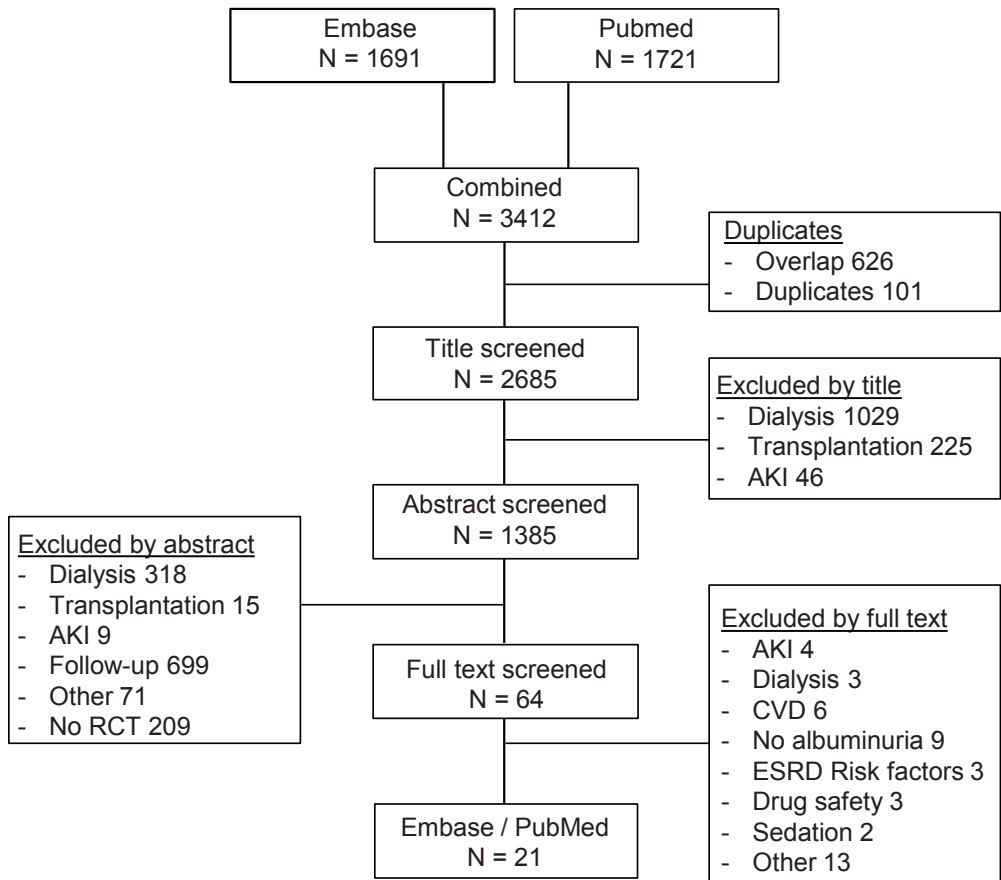
Chronic kidney disease (CKD) receives growing attention as a major public health concern. Clinical practice guidelines advocate early detection and appropriate treatment based on the rationale that intervention in the early course of disease may be more advantageous.<sup>1</sup>

<sup>2</sup> To establish drug efficacy in clinical trials of progression of CKD doubling of serum creatinine and end-stage renal disease are used as clinical endpoints. However, progression of kidney disease to ESRD takes many years to manifest. Clinical trials enrolling patients at early stages of disease would therefore require a long follow-up or an impractical large sample size to establish drug efficacy. The use of surrogate endpoints may be a solution to this problem. However, before a surrogate endpoint is used in clinical trials rigorous validation is required. The criteria for validation are defined in the 'statistical principles of clinical trials' of the International Conference of Harmonization.<sup>3</sup> First, prognostic evidence of the surrogate end point with patient outcome must be available. Second, a biologically plausible relationship between the surrogate and outcome should exist, and third, clinical trial data must demonstrate that the effect of interventions that change the surrogate end point is directly associated with the same change in clinical outcomes. A typical example is blood pressure, because high blood pressure is associated with cardiovascular risk and reduction of blood pressure, by whatever means, lowers cardiovascular risk.

Albuminuria has been proposed as a surrogate endpoint in clinical trials of CKD progression.<sup>4</sup> Multiple clinical studies have shown a strong and independent association between albuminuria and ESRD,<sup>5</sup> while experimental studies have documented the causal mechanisms through which increased urinary albumin leakage aggravate kidney damage.<sup>6</sup> In addition, analyses from several clinical trials have shown that the initial treatment induced change in albuminuria predicts subsequent renal risk change.<sup>7-12</sup> Although the consistency of these studies support the validity of albuminuria as a surrogate, the correlation analyses from randomized controlled trials between changes in albuminuria and ESRD were conducted post-hoc and were no longer based on randomized comparisons. Therefore, the possibility that the lower risk of ESRD among patients with a reduction in albuminuria were caused by factors unrelated to the anti-albuminuric effect of the intervention cannot be excluded. To minimize this type of bias it is necessary to associate the placebo con-

trolled treatment effects on albuminuria with the placebo controlled treatment effects on ESRD. This approach requires a combined analysis of multiple randomized controlled trials. A combined analysis of multiple clinical trials allows assessment whether the reductions in albuminuria and ESRD are independent of the interventions that are used. If so, it would support the idea that the reduction in albuminuria is the determinant of renoprotection rather than the intervention per se. Therefore, the aim of this study was to conduct a systematic review and meta-analysis to reliably examine the treatment effects of various interventions on an initial change in albuminuria as a predictor of the treatment effect on ESRD.

**Figure 1.** Identification process for eligible studies



## Results

### Literature search and characteristics of studies

The combined literature search in EMBASE and MEDLINE via PubMed yielded 3412 articles, of which 626 articles were duplicates identified in both databases. Sixty-four articles were reviewed in full text on the basis of our inclusion criteria (Figure 1). Of these, 21 randomized clinical trials provided information on 78,342 patients and 4183 ESRD events and were eligible for inclusion. All trials were published in peer-reviewed journals. The majority of other studies identified by our search but not included in the meta-analysis were randomized clinical trials in dialysis, renal transplant or acute kidney populations, or had insufficient patient follow-up to be eligible.

Table 1 summarizes the characteristics of the included studies. These were reported between 1994 and 2013, with a sample size that ranged from 224 to 25620 participants and total events accrued from two to 2141. Twelve studies were international multicentre trials,<sup>13-24</sup> five studies were conducted in North America,<sup>25-28</sup> two studies in China,<sup>29, 30</sup> one study in Italy,<sup>31, 32</sup> and one study in Japan and Hong Kong.<sup>33</sup> Five studies assessed the effects of an angiotensin converting enzyme inhibitor (ACEI),<sup>13, 25, 27, 30, 31</sup> four studies an angiotensin receptor blocker (ARB),<sup>18, 21, 33, 34</sup> one study the effect of an ACEI or ARB,<sup>29</sup> one study the effect of a combination of an ACEI with a diuretic,<sup>14</sup> three studies assessed the effect of dual renin-angiotensin-aldosterone-system (RAAS) blockade with either combined ACEi and ARB,<sup>19, 26</sup> or a direct renin inhibitor as adjunct to ACEi or ARB,<sup>15</sup> two studies a lipid lowering intervention,<sup>17, 22</sup> two studies dietary protein restriction,<sup>28</sup> two studies intensive blood pressure control,<sup>16, 20</sup> and one study a glycosaminoglycan.<sup>23</sup> The average age of the study participants ranged from 12 to 68 years and the proportion of men ranged from 28 to 93%. A total of eleven studies reported albuminuria as albumin:creatinine ratio which ranged from 7.2 to 1900 mg/g. Ten other studies measured total proteinuria which ranged from 120 to 3500 mg/24-hour. The mean baseline eGFR ranged from 19 to 92 ml/min/1.73m<sup>2</sup>. All but one study provided information about the proportion of patients with diabetes (range 0 to 100%). Seven studies included patients with diabetic nephropathy,<sup>15, 18, 21, 23, 26, 27, 33</sup> and ten with non-diabetic nephropathy.<sup>13, 16, 20, 22, 25, 28, 29, 31, 32</sup> There were some minor differences in the definition of ESRD across studies. All studies defined ESRD as the need for chronic dialysis or transplantation. Four studies included a fixed serum creatinine threshold in the definition of ESRD,<sup>17, 18, 23, 33</sup>

**Table 1.** Characteristics of randomized controlled trials reporting the effects of various agents

<b>Acronym (year)</b>	<b>N of patients</b>	<b>N of ESRD events</b>	<b>Inclusion criteria</b>	<b>Active Treatment</b>
AASK (2001) <sup>25</sup>	1094	179	Afro-American with hypertensive nephrosclerosis	Ramipril
ADVANCE (2001) <sup>14</sup>	11140	46	Type 2 diabetes at CV risk	Perindopril and Indapamide
AIPRI (1999) <sup>13</sup>	583	2	Renal insufficiency	Benazepril
ALTITUDE (2012) <sup>15</sup>	8561	234	Type 2 diabetes at cardio-renal risk	Aliskiren (+ ACEi or ARB)
BENAZEPRIL (2009) <sup>30</sup>	224	63	Non-diabetic nephropathy	Benazepril
CSG-Captopril (2006) <sup>27</sup>	409	51	Type 1 diabetes and nephropathy	Captopril
ESCAPE (2009) <sup>16</sup>	385	56	Children with nephropathy	Intensive BP control
FIELD (2005) <sup>17</sup>	9795	47	Type 2 diabetes at cardiovascular risk	Fenofibrate
IDNT (2001) <sup>18</sup>	1715	287	Type 2 diabetes and nephropathy	Irbesartan
MDRD A (1994) <sup>28</sup>	584	58	Non-diabetic nephropathy with GFR 25-55 ml/min	Low protein diet
MDRD B (1994) <sup>28</sup>	255	136	Non-diabetic nephropathy with GFR 13 – 24 ml/min	Low protein diet
ONTARGET (2008) <sup>19</sup>	25620	98	CV risk with end organ damage	Telmisartan and ramipril
ORIENT (2011) <sup>33</sup>	566	152	Type 2 diabetes and nephropathy	Olmesartan
VA-NEPHRON D (2013) <sup>26</sup>	1448	70	Type 2 diabetes and nephropathy	Losartan (+ Lisinopril)
REIN (1997/1999) <sup>31, 32</sup>	352	73	Non-diabetic nephropathy	Ramipril
REIN 2 (2005) <sup>20</sup>	338	72	Non-diabetic nephropathy	Intensive BP control with felodipine
RENAAL (2001) <sup>21</sup>	1513	341	Type 2 diabetes and nephropathy	Losartan
ROAD (2007) <sup>29</sup>	339	26	Non-diabetic nephropathy	Anti-albuminuric dose of ACEi or ARB
SHARP (2011) <sup>22</sup>	6247	2141	Diabetic and non-diabetic nephropathy	Simvastatine and Ezetimibe
SUN MACRO (2012) <sup>23</sup>	1248	21	Type 2 diabetes and nephropathy	Sulodexide
TRANSCEND (2008) <sup>34</sup>	5926	10	Patients intolerant to ACE inhibitors at CV risk	Telmisartan

on albuminuria and end-stage renal disease

<b>Control</b>	<b>Age (years)</b>	<b>Female (%)</b>	<b>eGFR (ml/ min/1.73m<sup>2</sup>)</b>	<b>Albuminuria (mg/g)</b>	<b>Systolic BP (mmHg)</b>	<b>Albuminuria change (%)</b>
Metoprolol or Amlodipine	54.6	38.8	45.6	120.0	150.4	-23.3
Placebo	66.0	42.5	72.2	15.0	145.0	-18.9
Placebo	51.0	72.0	42.6	1800.0	143.0	-30.4
Placebo (+ ACEi or ARB)	64.5	31.9	57.0	207.0	137.3	-11.0
Placebo	44.7	49.6	26.1	1700.0	152.4	-28.8
Placebo	34.5	47.0	59.0	2746.9	138.5	-25.6
Conventional BP control	11.5	40.7	45.9	1200.0	118.3	-16.4
Placebo	62.2	7.2	92.0	10.0	140.5	-13.9
Placebo or Am- lodipine	58.8	32.0	41.1	1900.0	159.0	-28.0
Conventional protein diet	52.0	40.0	38.6	200.0	131.0	-13.0
Conventional protein diet	52.0	40.0	18.5	710.0	133.0	-14.6
Ramipril or Tel- misartan	66.4	26.8	69.2	7.2	141.8	-7.1
Placebo	59.2	30.9	42.9	1695.1	141.2	-32.1
Placebo (+ Lisinopril)	64.6	27.4	53.7	852.0	137.0	-19.6
Placebo	49.5	23.6	42.9	3500.0	145.9	-29.3
Conventional BP control	53.8	25.1	35.0	2900.0	136.7	-11.4
Placebo	60.0	36.8	35.0	1249.1	152.5	-31.9
Conventional BP dose of ACEi or ARB	50.9	37.2	30.6	1800.0	150.2	-16.0
Placebo	62.0	37.4	26.6	206.5	139.0	-1.8
Placebo	63.0	39.2	31.4	1389.3	138.0	-1.3
Placebo	66.9	43.0	71.7	5.9	141.0	-28.0



while three other studies also included renal death to the definition of ESRD.<sup>14, 15, 17</sup> Study follow-up period ranged between eleven to 56 months. Quality assessment revealed that all trials used a concealed treatment allocation, provided information on the participant flow throughout the study, compared baseline characteristics, and analysed according intention-to-treat (Supplement Table 1). Across all published trials the average Jadad score was 4.7 (range 4 - 5). Formal statistical testing did not suggest the presence of publication bias (Begg's test  $P=0.81$ ; Supplement Figure 1).

**Supplementary Table 1.** Quality analyses of the trials included in the meta-analysis using the JADAD scale

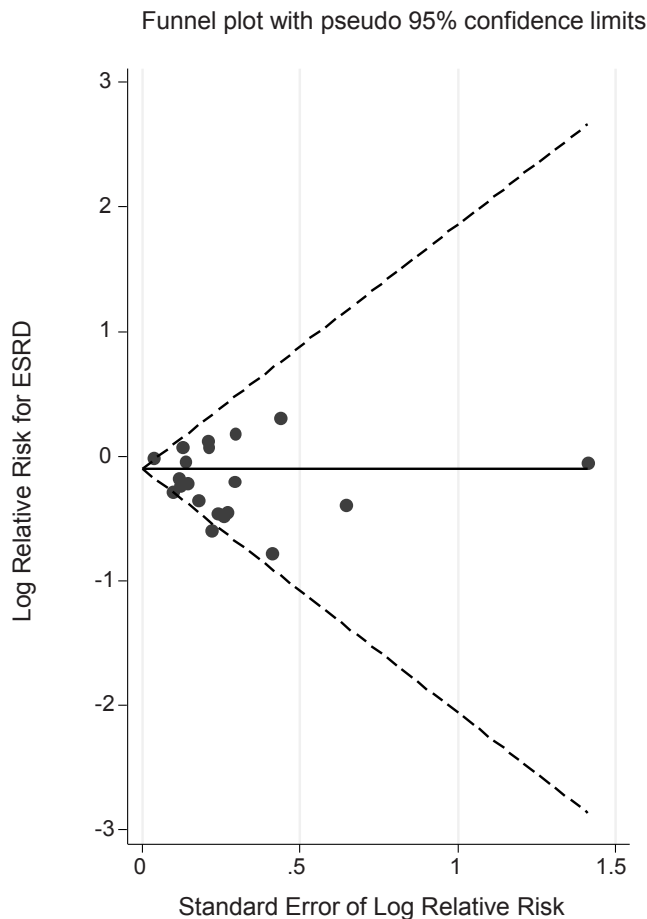
Trial (year)	Was the study randomized	Appropriateness and description of the randomization sequence	Was the study double blinded	Appropriateness and description of the blinding procedure	Description of drop outs and withdrawal	Jadad Score
AASK (2001)	1	0	1	1	1	4
ADVANCE (2001)	1	1	1	1	1	5
AIPRI (1999)	1	0	1	1	1	4
ALTITUDE (2012)	1	1	1	1	1	5
BENAZIPRIL (2009)	1	1	1	1	1	5
CAPTOPRIL (2006)	1	1	1	1	1	5
ESCAPE (2009)	1	1	1	1	1	5
FIELD (2005)	1	1	1	1	1	5
IDNT (2001)	1	1	1	1	1	5
MDRD A (1994)	1	0	1	1	1	4
MDRD B (1994)	1	0	1	1	1	4
ONTARGET (2008)	1	1	1	1	1	5
ORIENT (2011)	1	1	1	1	1	5
VA Nephron D (2013)	1	0	1	1	1	4
REIN (2000)	1	1	1	1	1	5
REIN 2 (2005)	1	1	1	1	1	5
RENAAL (2001)	1	1	1	1	1	5
ROAD (2007)	1	1	1	1	1	5
SHARP (2011)	1	1	1	1	1	5
SUN MACRO (2012)	1	0	1	1	1	4
TRANSCEND (2008)	1	1	1	1	1	5

### Effect of treatment on albuminuria and ESRD

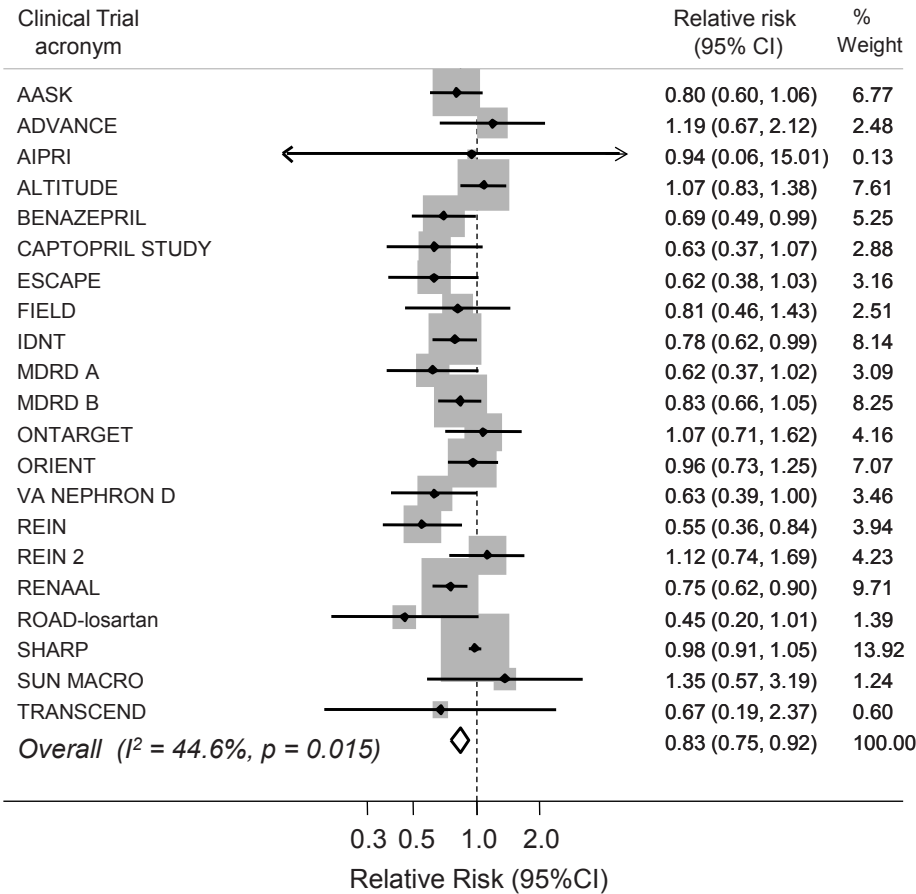
The average albuminuria reduction between baseline and first albuminuria measurement was 19.2%. There was substantial variability in the treatment effects on albuminuria across all trials, ranging from -1.3% to -32.1%. Overall, active treatment reduced the risk of ESRD by 17% (95%CI 8 to 25%) compared with control regimens (Supplement Figure 2). A large variability in treatment effects on ESRD was observed ranging from -55% to +35% across all studies. Formal statistical testing suggested significant heterogeneity in the magnitude of the treatment effect ( $\chi^2=36.1$ ;  $P=0.015$ ;  $I^2 = 44.6\%$ ).

2

**Supplementary Figure 1.** Funnel plot for assessment of publication bias.



**Supplementary Figure 2.** Treatment effects on albuminuria across all trials.  
Shown are the relative risk and the 95% confidence interval



**Association between treatment effects on albuminuria and ESRD**

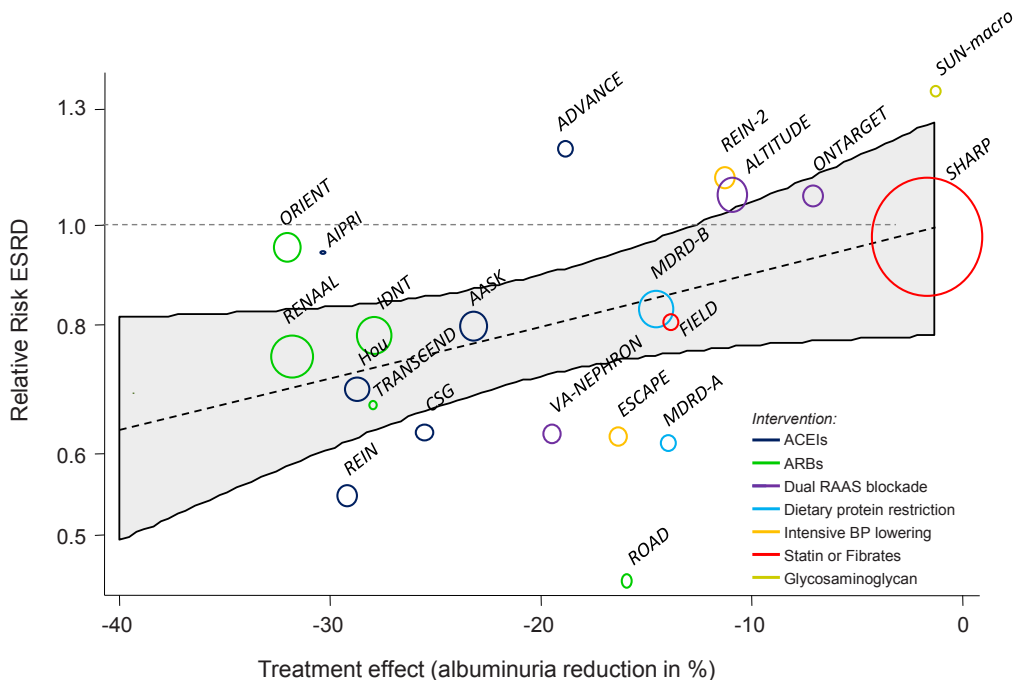
The association between drug effects on albuminuria and ESRD was analyzed by meta-regression. This revealed that the treatment effects on albuminuria significantly correlated with the treatment effects on ESRD. For each 30% reduction in albuminuria the risk of ESRD decreased by 23.7% (95%CI 11.4 to 34.2%;  $P=0.001$ ; Figure 2).

Figure 3 shows that the association between drug induced changes in albuminuria and ESRD were consistent in various subgroup analyses. For each 30% reduction in albuminuria by drugs that intervene in the renin-angiotensin-aldosterone-system (RAAS) the risk of ESRD decreased by 32% (95%CI -55 to +2) compared to 39% (95%CI -65 to +9) with drugs that do not intervene in the RAAS (Figure 3). There was no evidence to suggest a statistically significant difference in the association according to the duration of follow-up, size of the study,

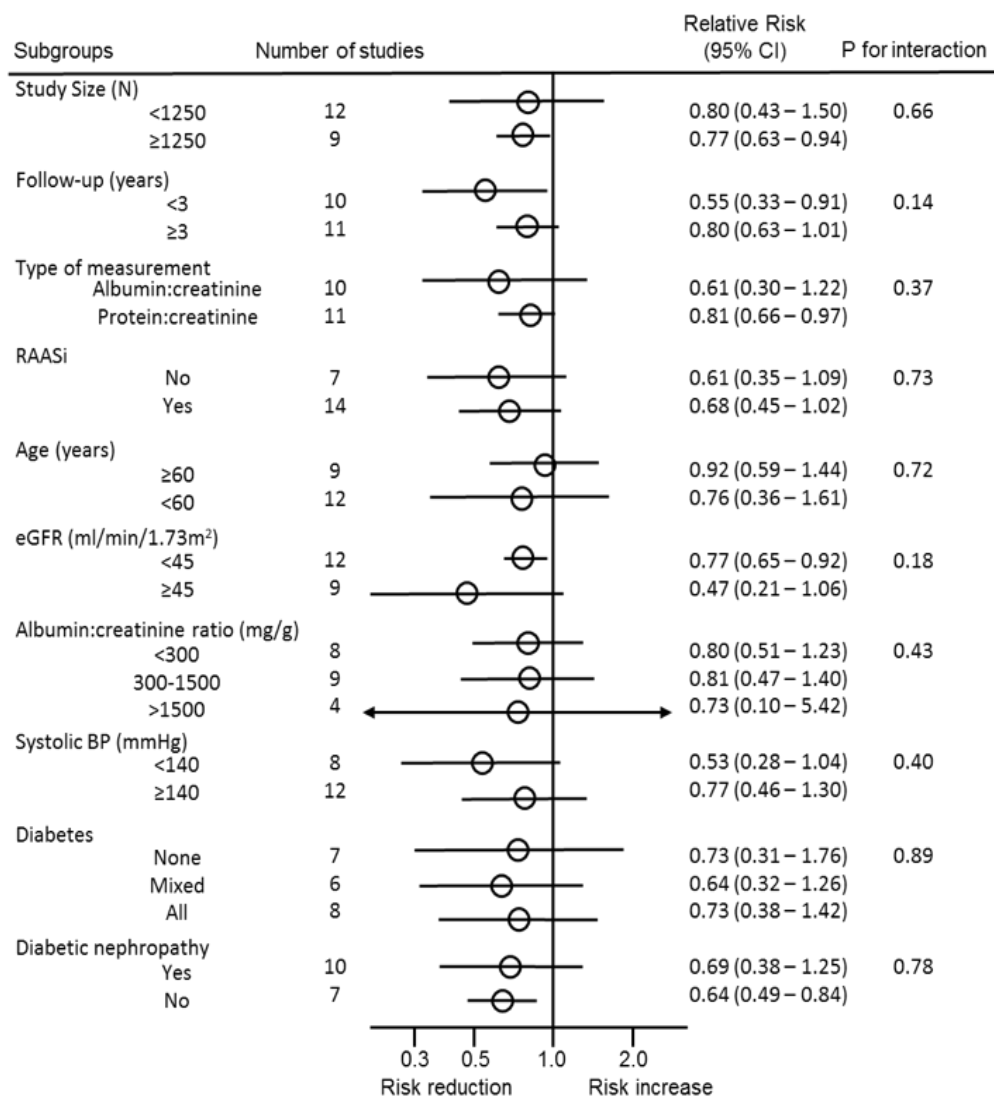
baseline albuminuria, eGFR, systolic blood pressure or between populations with diabetic nephropathy or non-diabetic nephropathy. Finally, a sensitivity analysis excluding the SHARP trial, that contributed a large number of events to the meta-analysis, did not alter the conclusions. For each 30% reduction in albuminuria the reduction in risk of ESRD was 27.4% (95%CI 0.7 to 46.9%;  $P=0.046$ ). In addition, a sensitivity analysis that excluded trials with only cardiovascular risk populations<sup>14, 17, 19, 24</sup> provided similar results: per 30% reduction in albuminuria the reduction in risk of ESRD was 24.6% (95%CI 11.6 to 35.7%;  $P=0.002$ ). The effect estimate was again similar to our main analysis when trials with albuminuria measurements at  $\geq 24$ -months follow-up were excluded (Hazard ratio for ESRD 24.8% (95%CI -11.6 – 49.2%;  $P=0.11$ ).

2

**Figure 2.** Univariate meta-regression exploring the association between the placebo controlled treatment effect on albuminuria and the placebo controlled treatment effect on ESRD events. Different type of interventions are indicated by different colors. The size of each circle is inversely proportional to the standard error of the treatment effect on ESRD.



**Figure 3.** Subgroup analysis for the effect of various interventions on albuminuria and ESRD events. Circles represent estimates of treatment effect on ESRD per 30% reduction in albuminuria. The horizontal line represents the 95% confidence interval. The p interaction tested the consistency of the association in subgroups.



## Discussion

Albuminuria has been proposed as a surrogate endpoint in clinical trials of CKD progression. However, there is persistent uncertainty about the validity of albuminuria to substitute for hard clinical endpoints which hamper its broad acceptance and application in daily practice of drug development, registration and drug use. In this meta-analysis of randomized controlled trials, we have demonstrated a statistically significant association between drug effects on albuminuria and ESRD. The associations appear to be consistent across a range of drug classes used in the included studies and various patient characteristics. These results suggest that albuminuria could be a valid substitute for ESRD and support designing trials with different albuminuria targets to prospectively establish the validity of albuminuria as surrogate endpoint.

Recent trials demonstrating that the drugs of investigation decreased albuminuria but did not decrease risk of ESRD fuelled discussions about the validity of albuminuria as a surrogate endpoint. Apart from the possibility that the increased risk of ESRD in these trials may be related to unintended off-target effects of the tested interventions,<sup>35, 36</sup> our meta-analysis also unambiguously demonstrates that the reductions in albuminuria observed in these trials were too small to translate into clinical meaningful benefits. For example, in the ALTITUDE trial, active treatment with the direct renin inhibitor aliskiren decreased albuminuria by 11% at month 6.<sup>15</sup> According to our meta-analysis this would only translate into 8% reduction of ESRD. Similarly, in the ONTARGET trial dual RAAS blockade decreased albuminuria by 7%,<sup>19</sup> a magnitude unlikely to translate into clinically relevant reductions in risk of ESRD. For new interventions a 30% reduction in albuminuria on top of guideline recommended care seems necessary to confer a realistically detectable renoprotective treatment effect.

The observed association between the treatment effect on albuminuria and ESRD were similar for various drug classes or dietary interventions. While most of the studies tested drugs that intervened in the RAAS, the strength of the association between reductions in albuminuria and ESRD was not different with other interventions that decreased albuminuria. Moreover, the associations were consistent in various sub-populations with different patient characteristics or underlying diseases supporting the generalizability of the results. Specifically, the strength of the association was not modified by baseline albuminuria, suggesting that reducing albuminuria both in the micro- and macroalbuminuria range is associated with renoprotection. We rec-

ognize however that the statistical power to reliably compare different drug classes as well as some sub-populations was small. Nevertheless, the results of this analysis demonstrate that the significant heterogeneity observed in the treatment effects on ESRD correlates with the heterogeneity in the treatment effects on albuminuria suggesting that the short-term treatment effect on albuminuria predicts the long-term treatment effect on ESRD.

The results of this study are generalizable to the populations and interventions included in this study. Although our results were consistent in various subgroups we cannot generalize to other populations or interventions. This implies that long-term clinical trials are required for drugs with novel albuminuria lowering mechanisms of action to proof their renoprotective efficacy. We therefore propose that drug approval can be granted if a novel drug decreases albuminuria on the condition that subsequent long-term clinical trials using clinical endpoints confirm the beneficial effect. These trials can also characterize the safety of the new agent which often requires a much larger sample size than establishing drug efficacy in a surrogate outcome trial. These so-called conditional approval procedures thus balance timely access to novel interventions for patients while at the same time collecting and providing adequate evolving information about the benefits and risks.

Few studies have prospectively assessed whether targeting of albuminuria delays progression of renal disease. The ROAD trial in patients with IgA nephropathy demonstrated that a regimen with either an ACEi or an ARB targeted to achieve a maximal anti-albuminuric response is associated with a marked better renal survival compared to a fixed maximal anti-hypertensive dose of these agents.<sup>29</sup> The IDNT trial showed that irbesartan decreased albuminuria compared to amlodipine at similar blood pressure control and conferred renoprotection in patients with diabetes and nephropathy.<sup>18</sup> The SONAR trial (Clinical Trial identifier NCT01858532) will further define whether albuminuria is a valid surrogate and whether targeting of albuminuria confers renoprotection in patients with type 2 diabetes and nephropathy. In this trial, all eligible patients will start the trial with a six weeks treatment phase during which the albuminuria response to the endothelin antagonist atrasentan will be established. Subsequently, patients are randomly assigned to atrasentan or matched placebo based on their albuminuria response. The randomization will be stratified for the different albuminuria responses. Accordingly, the SONAR trial will determine in a placebo controlled manner whether the degree of albuminuria reduction with atrasentan is re-

lated to the degree of renoprotection. The trial will therefore further define whether albuminuria reduction is a necessary prerequisite for reducing renal morbidity and mortality.

The mechanisms through which albuminuria reduction delays renal disease progression is an area of great research interest. Since 1990 the hypothesis of a pathogenic role of altered glomerular permeability to macromolecules - and consequent protein overload to podocytes and tubular cells - in the pathogenesis and progression of glomerulosclerosis has been the matter of a lively debate.<sup>37</sup> Recent data suggest that albuminuria per se is not just a marker of renal damage but may have a causal role in renal disease progression as well.<sup>6</sup> Within the kidney, increased glomerular filtration of albumin and other plasma macromolecules (e.g. immunoglobulins, growth factors, complement components) increases the exposure of tubular cells to excessive albumin re-uptake in proximal tubular cells which in turn leads to the activation of multiple pathways that cause the release of vasoactive, inflammatory, and fibrotic substances.<sup>38, 39, 40</sup> Collectively, these processes result in tubulointerstitial damage and decreased nephron functionality.

Our results build upon a prior meta-analysis that sought to determine the validity of an early change in proteinuria as a surrogate endpoint for trials of kidney disease progression.<sup>41</sup> That meta-analysis included many small studies which were published prior to 2007. The meta-analysis showed that when all studies were grouped together by type of intervention, the treatment effects on proteinuria and the renal outcome were consistent, in line with our findings.<sup>41</sup> However, when studies were analyzed individually, the trial-level analysis showed no clear correlation between early changes in proteinuria and risk of doubling serum creatinine or ESRD likely reflecting insufficient variation in drug effects and/or statistical power. Our meta-analysis pre-specified to only include trials with more than 1000 patient-years follow-up and/or more than 50 ESRD events to obtain sufficient statistical power, and included all large trials which were published after 2007. Analyzing the sub-group of studies included in the study by Inker et al. did not change our results. The differences between the previous and our meta-analysis may be explained by the difference in included studies with exclusion of small studies in the prior analysis and inclusion of large recent trials in our meta-analysis. Additionally, the correlation between errors in treatment effects on albuminuria and ESRD may have led to an overestimation of the reported association in the present meta-analysis. Since individual patient data was not available for all studies we were unable to adjust for this.



Although we found a direct relation between drug-induced albuminuria reduction and renal outcome, we do not postulate that each drug-associated albuminuria reduction will ultimately result in renal protection. Several recent studies (in particular dual RAAS blockade) have shown no renal protection despite albuminuria reduction.<sup>15, 26</sup> Just like with other established surrogates, for example blood pressure or cholesterol, a drug induced fall will not offer cardiovascular/renal protection in case that the intervention also induces negative effects (e.g. hypotension, hyperkalemia). Thus, albuminuria reduction can only be a substitute for renal protection when the intervention is otherwise safe.

This study has limitations. First, studies included in the meta-analysis were not designed to target albuminuria leading to potential less rigorous measurements and variability in treatment effects on this biomarker. Indeed, the individual trials showed considerable spread around the regression line. However, a similar spread across large clinical trials have been shown for other valid and clinically used surrogate endpoints such as blood pressure and cholesterol.<sup>42, 43</sup> It may be possible that the total exposure to albuminuria, as reflected by the area under the albuminuria curve, may be a better predictor of renal risk change than the change between two measurements. Second, some patients were lost to follow-up or reached an event prior to the post-baseline albuminuria measurement which could have influenced the results. Finally, albuminuria was assessed after 24 months in five studies whereas in all other studies albuminuria was assessed within 6 months. As the effects of most anti-albuminuric interventions are present directly after treatment initiation we assumed that the treatment effect at 24 months will likely resemble the effect after 6 months although we cannot verify this assumption. However, a sensitivity analysis that excluded the five studies provided similar results. In conclusion, short term albuminuria reduction is associated with long term renal protection across different interventions and populations. When considered in combination with observational studies demonstrating a strong association between the albuminuria level and risk of kidney outcomes, and experimental studies demonstrating the role of plasma macromolecules in causing kidney damage, we propose that albuminuria can be recommended as surrogate endpoint in clinical trials for initial drug approval on the condition that long-term follow-up trials on clinical endpoints confirm the renoprotective effect of the agent.

## Concise Methods

### Data sources and searches

We performed a systematic review of the available literature according to the Quality of Reporting of Meta-Analyses (QUORUM) guidelines for the conduct of meta-analyses of intervention studies. Relevant studies were identified by computerized searches from the following data sources: MEDLINE via PubMed (from 1950 through April 2014) and EMBASE (from 1950 through April 2014) using relevant text words and medical subject headings that included all spellings of proteinuria or kidney diseases, drug therapy or drug effects, and ESRD (supplement table 2). The term ‘albuminuria’ is used throughout this article and indicates abnormal excretion of urinary proteins including albumin. The search was limited to randomized controlled trials but was without language restriction. Reference lists from identified trials and review articles were manually scanned to identify any other relevant studies. Search of the clinicaltrials.gov website was also performed to identify randomized trials that were registered as completed but not yet published. Requests for original data were made directly by contacting authors or principal investigators.

**Supplementary Table 2.** Search strategy

Database	Search terms
PubMed	proteinuria [mh] OR kidney diseases[mh] AND (drug therapy[sh] OR drug effects[sh]) AND (endstage renal disease OR end-stage renal disease OR dialysis OR ESRD OR renal replacement therapy) AND randomized controlled trial[pt] AND humans[mh] NOT (comment[pt] OR letter[pt] OR editorial[pt])
EMBASE	‘proteinuria’/exp OR ‘kidney disease’/exp AND ‘chemicals and drugs’/exp AND (‘end stage renal disease’/exp OR ‘dialysis’/exp OR ‘renal replacement therapy’/exp OR ‘end stage renal disease’:ab,ti OR ‘endstage renal disease’:ab,ti OR ‘end-stage renal disease’:ab,ti OR ‘dialysis’:ab,ti OR ‘esrd’:ab,ti OR ‘renal replacement therapy’:ab,ti) AND [randomized controlled trial]/lim AND [humans]/lim AND [article]/lim

### **Study selection**

The literature search, data extraction and quality assessment were conducted independently by two authors using a standardized approach (JH and TFK). All completed randomized controlled trials with more than 1000 patient-years follow-up or more than 50 ESRD events and assessing the effects of different interventions on albuminuria and ESRD were eligible for inclusion. Outcomes analysed was “ESRD” defined as chronic dialysis or renal transplantation or renal death defined as death attributable to renal failure or need for renal replacement therapy with no dialysis or renal transplantation applied in the definition of ESRD

### **Data extraction and Quality assessment**

Data extracted included patient characteristics (mean age, gender distribution, eGFR, albuminuria, systolic blood pressure, diabetes status, cardiovascular disease status), follow-up duration, rates of outcome events, type and dose of interventions. The initial albuminuria response was defined as the percentage change in albuminuria from baseline to the first measured albuminuria level during the trial. Summary measures of effects on ESRD outcomes were extracted from each study. Any disagreement in abstracted data was adjudicated by a third reviewer (HJLH). The Quality of the included studies was assessed by the Jadad score.<sup>44</sup> The Jadad score is a tool used to systematically grade the quality of RCT's based on the presence and appropriateness of the blinding procedure, randomization and handling of drop-out and loss to follow-up.

### **Data synthesis and analysis**

Individual study relative risks (RR) and 95% confidence intervals (CIs) were extracted before data pooling. Summary estimates of relative risk ratios were obtained using a random effects model. The percentage of variability across studies attributable to heterogeneity beyond chance was estimated using the  $I^2$  statistic.<sup>45</sup> Univariate meta-regression was used to assess the association between the drug effect on albuminuria and ESRD. The consistency of the association was assessed by comparing summary results obtained from subsets of studies grouped by type of intervention (renin-angiotensin-aldosterone-system inhibitors (RAASi) vs. non-RAASi), number of enrolled patients, duration of follow-up, duration until first albuminuria measurement and patient characteristics. For the purpose of subgroup analyses by baseline albuminuria, studies were categorized by study

median data for albumin:creatinine ratio. Some studies measured total protein excretion. To convert to albumin:creatinine ratio, study average total protein excretion was multiplied by 0.6 as total daily protein excretion of 0.5 g/day approximate 300 mg/g albumin:creatinine ratio.<sup>47</sup> Potential publication bias was assessed using the Begg's test and represented graphically using funnel plots of the natural log of the relative risk versus its standard error. A two-sided p-value of less than 0.05 was considered statistically significant for all analyses. All statistical analyses were performed with STATA, version 9.2 (Stata, College Station, Texas).

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## Disclosures

Dick de Zeeuw is consultant for and received honoraria (to employer) from AbbVie, Astellas, AstraZeneca, BMS, Chemocentryx, J&J, Hemocue, Novartis, Reata, Takeda, Vitae. Hiddo Lambers Heerspink is consultant for and received honoraria (to employer) from AbbVie, Astellas, J&J, Reata, Vitae.

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